

1 1. A method of identifying a compound that
2 modulates JNK3 expression, the method comprising:
3 incubating a cell that can express a JNK3 protein
4 with a compound under conditions and for a time sufficient
5 for the cell to express a JNK3 protein absent the compound;
6 incubating a control cell under the same conditions
7 and for the same time absent the compound;
8 measuring JNK3 expression in the cell in the
9 presence of the compound;
10 measuring JNK3 expression in the control cell; and
11 comparing the amount of JNK3 expression in the
12 presence and absence of the compound,
13 wherein a difference in the level of expression indicates
14 that the compound modulates JNK3 expression.

1 2. The method of claim 1, wherein the compound
2 decreases the expression of JNK3.

1 *Sub c2* 3. A method of identifying a compound that
2 modulates JNK3 activity, the method comprising:
3 incubating a cell that has JNK3 activity with a
4 compound under conditions and for a time sufficient for the
5 cell to express JNK3 activity absent the compound;
6 incubating a control cell under the same conditions
7 and for the same time absent the compound;
8 measuring JNK3 activity in the cell in the presence
9 of the compound;
10 measuring JNK3 activity in the control cell; and
11 comparing the amount of JNK3 activity in the presence and
12 absence of the compound,
13 wherein a difference in the level of activity indicates that
14 the compound modulates JNK3 activity.

1 4. The method of claim 3, wherein the compound
2 decreases JNK3 activity.

1 ~~5. A method of identifying a compound that~~
2 ~~modulates the binding of a JNK3 polypeptide to a substrate,~~
3 ~~said method comprising comparing the amount of a JNK3~~
4 ~~polypeptide bound to a substrate in the presence and absence~~
5 ~~of a selected compound, wherein a difference in the amount~~
6 ~~of binding of a JNK3 polypeptide to a substrate indicates~~
7 ~~that said selected compound modulates the binding of a JNK3~~
8 ~~polypeptide.~~

1 6. The method of claim 5, wherein the binding of a
2 JNK3 polypeptide to a substrate is decreased.

1 7. A method for generating a totipotent mouse cell
2 comprising at least one inactivated JNK3 gene, the method
3 comprising:
4 a. providing a plurality of totipotent mouse cells;
5 b. introducing into the cells a DNA construct
6 comprising a disrupted mouse JNK3 gene, wherein the JNK3
7 gene is disrupted by insertion of a nucleotide sequence into
8 the gene that prevents expression of functional JNK3;
9 c. incubating the cells such that homologous
10 recombination occurs between the chromosomal sequence
11 encoding JNK3 and the introduced DNA construct; and
12 d. identifying a totipotent mouse cell comprising
13 at least one inactivated JNK gene.

1 8. A method for generating a mouse homozygous for
2 an inactivated JNK3 gene comprising:
3 a. providing a totipotent mouse cell comprising at
4 least one inactivated JNK3 gene;

- 5 b. inserting the cell into a mouse embryo and
6 implanting the embryo into a female mouse;
7 c. permitting the embryo to develop into a neonatal
8 mouse;
9 d. permitting the neonatal mouse to reach sexual
10 maturity; and

11 e. mating two sexually mature mice of step d.
12 to obtain a mouse homozygous for the inactivated JNK3
13 gene(-/-), wherein the homozygous JNK3(-/-) mouse is
14 resistant to excitotoxic damage.

1 9. A method of treating a patient having or at risk
2 for a disorder involving excitotoxicity, the method
3 comprising administering to the patient a therapeutically
4 effective amount of a compound that inhibits JNK3
5 expression.

1 10. The method of claim 9, wherein the compound is
2 an antisense nucleic acid molecule.

1 11. The method of claim 9, wherein the disorder is
2 selected from the group consisting of Alzheimer's disease,
3 Huntington disease, ischemia, amyotrophic lateral sclerosis,
4 trauma, motorneuron disease, Parkinson's disease, or
5 epilepsy.

1 12. A transgenic non-human mammal having a
2 transgene disrupting expression of a JNK3 gene, the
3 transgene being chromosomally integrated into germ cells of
4 the mammal.

